Imaging protocol for patients in European SIOP Brain Tumour Studies (2017)

Imaging evaluation of primary tumours of the CNS and possible CNS dissemination is core to their management in children. Patients entering therapeutic trials must therefore meet and adhere to the minimum imaging requirements for recruitment into the various studies. The most important issue is comparability of the pre-operative, post-operative MRI examinations and subsequent follow up studies. If the baseline MRI does not conform to these requirements it should either be repeated pre-operatively or the post-operative imaging should be performed in a way (e.g. additional sequences to the standard protocol) that will ensure comparability with the preoperative MRI. This is especially important for brain tumours that show little or no enhancement. In these cases the T2, FLAIR and pre-contrast T1 images must be comparable.

One of the main challenges involved in designing an imaging protocol is the variation in imaging resources across all centres i.e. manufacturer/field strength of MR scanners, availability of newer hardware/sequences, advance imaging capabilities and expertise, radiology department workflow and personnel. For maximum compliance with a protocol a balance needs to be struck between practicality and image quality.

This protocol has been developed by the European SIOP Brain Tumour Imaging Group and is based on consensus and evidence from earlier clinical trials. The protocol has evolved over the past few years and is being updated in response to changes in imaging practices and the specific needs of the various clinical trials. . The protocol comprises a mandatory set of sequences which is a minimum requirement and additional sequences including multi-modal advance MR imaging which are recommened. Standard guidance on follow up imaging and response assessments will be amended where necessary for individual trials.

1.MRI protocol

1.1 Brain imaging

Essential sequences

1 to1.5 tesla scanner

Sequence	**Technique**	**Plane**
T_1W	2D SE, TSE/FSE	Axial (along AC-PC axis)
T_2W	2D SE, TSE/FSE	Axial
FLAIR	2D TSE/FSE	Axial or coronal
T_1W + Contrast	2D SE, TSE/FSE	Axial, coronal and sagittal
DWI with ADC	2D EPI	Axial

3 tesla scanner

Sequence	**Technique**	**Plane**
T_1W	3D gradient echo	Axial or sagittal
T_2W	2D SE, TSE/FSE	Axial
FLAIR	2D TSE/FSE	Axial or coronal
T_1W + Contrast	2D SE, TSE/FSE	Axial
T_1W + Contrast	3D gradient echo	Axial or sagittal
DWI with ADC	2D EPI	Axial

3D gradient echo (GRE) sequence is the inversion recovery GRE sequence (MPRAGE/ IR SPGR/Fast SPGR/ 3D TFE/3D FFE)

2D sequences :Slice thickness≤ 4mm and slice gap ≤ 1mm (10 % of slice thickness is desirable). For very small lesions consider a slice thickness of 3mm or less.

3D sequence : Slice thicknesss ≤ 1mm with no slice gap. An isotropic voxel resolution of 1mm x 1 mm x 1 mm is desirable depending on scanner capability

Resolution parameters : Field of view – 230 mm(range 220-250 mm depending on head size); Matrix size - minimum 256 (512 is desirable for better resolution; 96- 128 for EPI sequences).

Some centres perform T1 FLAIR, T1 inversion recovery (IR) or T1 gradient echo instead of T1 SE sequence due to its suboptimal quality on 3T scanners. This is acceptable as long as the diagnostic quality of the imaging is not compromised and the same sequence is used consistently for the individual patient.

There are increasing concerns of longterm gadolinium deposition and the use of macrocyclic gadolinium based contrast agents is recommended.

Squences on 1.5T or 3T that may provide additional information

Sequence	**Technique**	**Plane**
T_1W	3D gradient echo (on 1.5T)	Axial or sagittal
FLAIR	3D gradient echo*	Axial or sagittal
Heavily weighted T_2W	2D or 3D CISS / B FFE/ FIESTA**	Axial or coronal or sagittal
Advanced MRI	DTI, perfusion & spectroscopy***	

Slice thicknesss for 3D sequences ≤ 1mm with no slice gap. An isotropic voxel resolution of 1mm x 1 mm x 1 mm is desireable depending on scanner capability.

*3D FLAIR can be used instead of 2D FLAIR but not if 2D sequences have been used for the same individual on previous occasions.

** The heavily weighted T2 W sequence localised to a region of interest is useful in assesment of lesions (in particular poorly/non enhancing) within the extra axial space or along the parenchymal surface.

*** Please refer to section 5.

1.2 Spine imaging:

Essential

Sequence	Technique	Parameter	Plane
T_1W + Contrast	2D SE/ TSE	Slice thickness ≤3mm Slice gap <0.5mm	Sagittal whole spine (entire dural sac)
T_1W + Contrast	2D SE/TSE or 3D gradient	Slice thickness 4-5 mm No slice gap	Axial –suspicious areas*

Squences that may provide additional information

Sequence	Technique	Plane
T_2W	2D SE/ TSE	Sagittal whole spine
T_2W	2D SE/TSE	Axial –suspicious areas
Heavily weighted T_2W	2D or 3D CISS / B FFE/ FIESTA**	Sagittal ±axial

*Physiological veins over the surface of the cord can be mistaken for nodules of dissemination and therefore **axial slices** without gaps (slice thickness should be 4 or 5 mm) are essential **for all suspicious areas**.

1.5 T is preferred to 3T for spinal imaging as the quality on older 3T systems is often inferior and more unpredictable. More recent generation 3T scanners now enable good, diagnostic quality spinal imaging but there must be a low threshold to reimage the spine on a 1.5 T scanner if it is of a suboptimal quality.

As fat suppression often leads to artefacts and is not necessary for the delineation of meningeal disease it should not be used routinely.

2.Tumour measurement

As volumetric measurement tools are not available at all centres, the tumour volume is calculated using the (ellipsoid volume) formula A x B x C x ½ where A, B and C are the maximum dimensions in the standard anteroposterior, transverse and craniocaudal planes. Imaging. 3D-volumetric calculations may be performed additionally. These volume calculations are the basis for follow-up evaluation and every effort should be made to ensure the highest possible accuracy. It is desirable to save the measurements as annotated images if possible.
If there are multiple lesions, the sum of the 5 largest lesions must be obtained. This will need further validation and may change in the future.

Please note that the measurement guidelines may be altered in some trials where 2D measurements in the axial plane or different measurement methods for the 3 dimensions may be employed.

3. Early post operative imaging

Optimal evaluation is made within the first 48 hours following surgery. As non-specific intracranial enhancement is often seen after 3 days following surgery the postoperative MRI must be obtained within this time. However, even within this time false positive nodular enhancement can be seen with haemostatic materials and following electrocoagulation. It is therefore prudent to carefully evaluate the pre- and post-contrast T1-weighted images in combination with the signal intensities on the T2-weighted and FLAIR sequences.

With increasing use of intraoperative MRI imaging the validity of the final intraoperative scan as baseline scan has been debated. Based on a single centre study and consensus it has been agreed that the final intraoperative MRI scan is acceptable as a base line provided it is from a 3T scanner (as it has been only validated on 3T) the SIOPE brain tumour protocol is followed, supervised by radiologist experienced in children's brain tumours and reported in consensus with the operating neurosurgeon. The preoperative and final intraoperative sequences must be comparable. On occasions where there has been further resection following the intraoperative scan, this will not qualify as a final intraoperative scan. A further scan after the extended resection with the full SIOP-E protocol should be performed. The final decision to use intraoperative MRI scans rests with the national reference radiologist/ radiology panel as the practices vary in different countries.

Comparability with the preoperative MRI is essential for the detection of residual tumour. The size of a possible residuum has to be measured in all three planes. If the residuum is best visible on T2-weighted images a second plane incorporating a T2-weighted or FLAIR sequence must be employed.
A residuum is considered to be any area of persisting pathological signal and/or enhancement that is comparable with the appearance of the pre-operative tumour. DWI is helpful to demonstrate any local surgical or ischaemic injury, which may influence enhancement patterns and tumour evaluation on subsequent examinations.
For the evaluation of residual tumour seen on imaging, the surgical report is often valuable and should be available.

Sequences for cranial and spinal imaging: Please refer to section 1

Please note if spinal MRI is performed post-operatively:
Non-specific subdural and intradural enhancement and possible intradural blood products and effusions may be identified on early post-operative imaging of the spine and must not be mistaken for meningeal dissemination. Where there is ongoing doubt or if intense subdural enhancement is seen, the spinal MRI should be repeated after 2 weeks for clarification.

4. Follow-up MRI:

Timing for follow-up MRIs should be planned according to the individual trial protocol.

Please refer to section 2 regarding tumour measurements.

If the tumour enhances uniformly, the post-contrast T1 should be used for the measurement of the diameters. For heterogeneously, poorly or non-enhancing tumours the dimensions on

T2/FLAIR or PD and pre-contrast T1 can be relevant. In some instances therapy related reduction of enhancement disproportionate to the change in tumour volume may be encountered. The best sequence cannot be predicted at the outset in these tumours. In these circumstances, it is useful to choose the initial sequence on which the tumour was measured or change the sequence (e.g. due to a change in contrast behaviour) and compare the tumour dimensions with the same sequence on the previous staging MRI to assess response.
In instances where the MRI findings are equivocal for tumour progression/resolution (pseudoprogression/pseudoresponse), an early follow up scan(s) may be required to evaluate for true progression/response.When true progression is confirmed, the initial scan which showed the abnormality should be considered as time of progression. In the paediatric neuro-oncology setting, pseudoresponse mainly refers to reduction of enhancement following anti-angiogenic therapy and the response assessment in this setting is based on measurement on the T2 and FLAIR sequences.

5. Definition of residual tumour

The evaluation of early postoperative imaging for residual tumour can pose challenges. As very subtle residual tumours may not be visible on imaging the presence / grading of residual tumour should be made in consensus with the neurosurgical report.

Residual tumour will be defined as follows (applies only for early postoperative MRI):

R0: No residual tumour on post-operative MRI in accordance with the neurosurgical report

R1: No residual tumour on MRI but description of a small tumour residuum by the neurosurgeon or if the neurosurgical result is unknown.

R2: Small residual tumour on MRI with the maximum diameter < 5mm in any plane or thin residual tumour covering the surgical margins like a ring or extending beyond the surgical margins.

R3: Residual tumour measurable and ≥ 5mm in all 3 planes.

R4: Size of the residual tumour unchanged or only minimally changed from the pre-operative status (e.g. after biopsy)

A thin line of enhancement can be physiological or reactive on early postoperative MRI and correlation with the non-contrast sequences for evidence of haemorrhage / tissue injury and detailed comparison with preoperative MRI may be required before considering the presence of residual tumour. If imaging is inadequate or the appearance of the surgical cavity is difficult to interpret the term “unclear” should be used. In some cases early follow up imaging in 2-4 weeks with additional sequences, better resolution parameters and additional planes may be necessary for further clarification.

6. Definitions for neuroradiological response evaluation:

6.1 Measurable tumours:

A measurable lesion is that which can be reliably followed up allowing for the slight variations of the scan planes. The defenition of measurable lesion is based on the historic practice of using 2D measurements on predominantly 2D imaging and mainly based on the RANO criteria. The current definition is based on the assumption that 2D sequences are predominantly used in a number of centres. This may change in the future when the quality of volumetric imaging is more reliable for tumour measurement and performed in all centres.

Mesaurable lesion:
Lesion visible in the 3 standard planes with a diameter of ≥ 10 mm in each plane. This is provided that the 2D image slice thickness+ gap is ≤ 5mm. If the slice thickness+ gap is > 5 mm, then the maximum diameter should be ≥ 2 times the slice thickness + gap.

Non measurable lesion also include lesions with poorly defined margins.

When there are multiple lesions, sum of the volumes of the 5 largest lesions are used.

6.2 Response criteria

CR (complete response): no evidence of residual or recurrent tumour or meningeal dissemination.

PR (partial response): Reduction of tumour volume ≥ 50% compared to the previous staging MRI. (The extent of meningeal dissemination can only be estimated and PR means considerable reduction of meningeal disease)

SD (stable disease): Tumour volume between ≤50% decrease in size and ≤25% increase in size compared to the previous staging MRI (no significant change of meningeal dissemination)
Nb. MR(minor response); This criterion is used in some trials for 50% to 25% decrease in tumour volume.

PD (progressive disease): increase of tumour volume of ≥ 25% or new lesion.

As highlighted in section 4, for measurable lesions, the sequence of choice for measurement cannot be predicted in advance and may require comparison of repeat measurement on the most reliable sequence on the current scan with a similar sequence on the prior/baseline scan for accurate response assessment.

Radiotherapy as a primary treatment may be associated with radiation induced reaction if there is measurable tumour growth after treatment. The combination with chemotherapy and radiotherapy may lead to temporary effects on imaging (enlarging contrast enhancing lesion, increased FLAIR/T2 abnormality) in up to 30-40% of cases, which are collectively known as pseudoprogression and may be mistaken for early true progression. If new enhancement or increase in residual tumour size occurs during the first 12 weeks after the end of irradiation

and within the irradiated field, do not consider this a true progression unless otherwise confirmed (either by histology or on a short interval follow up scan – after at least 4-6 weeks). If there is confirmed growth on the follow-up MRI, then the date of progression is ascribed to the first time point when tumour growth was documented.

7. Multi-Modal Advanced MRI

There is increasing experience in the use of a number of advanced MRI techniques and these may add useful information to the conventional MRI. The individual techniques should be thought of as complimentary and as such a multi-modal approach is most appropriate. We have developed and tested protocols which seek to provide a balance between quality of data and length of acquisition and at the same time give sufficient flexibility that they can be implemented on most MR scanners. MR spectroscopy (MRS) and Diffusion Tensor Imaging (DTI) methods are well established throughout the age range and the protocols for these are fairly well agreed. However, contrast injection perfusion imaging is less well established in children. We recommend Dynamic Susceptibility Contrast (DSC) – MRI at present, although there are still some areas of active development in the protocol particularly related to the contrast injection (see section below). The current protocols for these three methods are given in the parameter table below. We do recognise that there are centres that will use more advanced protocols and would encourage anyone who is doing this or considering it to contact the SIOPE – Brain Imaging Group so that we can share experiences and further develop protocols. Examples are: 1) Arterial Spin Labelling for measuring perfusion without injecting contrast. Whilst this has generated considerable interest, we feel that further experience is required in applying this technique to children's brain tumours, in particular its relationship with DSC-MRI, prior to recommending an international protocol. 2) Multi-b value DWI and the IVIM model for measuring perfusion without injecting contrast. 3) MRS imaging to investigate the heterogeneity of tumours.4) Functional brain connectivity via a steady state fMRI protocol especially in diencephalic syndrome. We are keen to carry out limited centre studies of such techniques.

Data Saving
It is important that data is saved in a way that it can be analysed in a quantitative manner. DICOM headers should not be altered in a manner which renders the data uninterpretable, which can happen when images are sent to some PACS systems or anonymised. Please seek advice if you are unsure.

Contrast Injection
For DSC-MRI, contrast (usually Gd-DTPA or Gd-DOTA) injection should be via a pump injector. Most centres will not use these via a central venous line and so injection will need to be via an intravenous cannula placed prior to the scan. In order to reduce the T1 effects we recommend giving a pre-bolus injection which is half of the full amount (i.e. 0.05mmol/Kg Gd) at least 2 minutes prior to the main injection which should also be 0.05mmol/Kg Gd, so that the total dose is 0.1mmol/Kg Gd. The rate of injection is standardised at 3ml/sec. This protocol has been used successfully in infants although there can be problems with the pump injector in very small ones, the protocol is subject to further development particularly in this age group.

Multimodal Protocol						22/09/2016		Version 2.3	SIOPE Brain Imaging Group		
Core Multimodal Protocol (Brain)											
Modality		MRS			Diffusion				Perfusion		
Description		SVS (short-TE)			DTI				DSC - T2*		
Sequence		PRESS			EPI				GRE		
		Param	Value	Value	Param	Value	Param	Value	Param	Value	Param	Value
Fixed		Field	1.5 T	3 T	Field	1.5T	Field	3T	Field	1.5T	Field	3T
		TR (ms)	1500	2000	FOV (mm)	240	FOV (mm)	211	FOV (mm)	240x240x95	FOV (mm)	240x240x10
		Vector length	2048	2048	Acq matrix	96x96	Acq matrix	96x96	Acq matrix	96x96x19	Acq matrix	96x96x30
		TE (ms)	30		Resolution	2.5 isotropic	Resolution (mr	2.2 isotropic	Orientation	axial	Orientation	axial
					Coverage	whole brain	Coverage	whole brain	Sense	2	Sense	2
					b factor	1000	b factor	1000	Temp resoln	1.49x60	Temp resoln	1.86sx60
Variable		TE (ms)		30 - 35	TR (ms)	min	TR (ms)	min	Sequence	FE-EPI	Sequence	FE-EPI
		VOI (ml)	3.4 - 8 (to fit tumour)	2.2 - 8 (to fit tumour)	TE (ms)	min (fix BW?)	TE (ms)	min (fix BW?)	TE (ms)	40ms	TE(ms)	40ms
		BW (kHz)	2 or 2.5 kHz	2 or 2.5 kHz	Grad dirs	15+	Grad dirs	15+	TR (ms)	min	TR(ms)	min
		Aves(WS)	128 - 256	64 - 196	NSA (b=0)	1(3)	NSA (b=0)	1 (3)	flip angle	20 deg	flip angle	20 deg
		Aves (W)	8 - 16	8 - 16	Speed-up	x2	Speed-up	x2	Injection rate	3ml/sec	Injection rat	3ml/sec
					Partial Fourier		Partial Fourier		Gd-DTPA	0.1mmol/Kg 50% as pre bolus	Gd-DTPA	0.1mmol/Kg 50% as pre bolus
Time (mins)	Set-up		3	3					2		2	
	Acq		3.4 - 6.6	2.3 - 6.7					2		2	
	Total		6.4 - 9.6	5.3 - 9.7	5		3		4		4	
	Total	minimum at 3T - 8.3 mins + DSC										

8. PET imaging

There is growing interest and evidence in the use of PET imaging to assess brain tumours in children at diagnosis and /or surveillance. The following section aims to serve as a guidance for the usage of PET in pediatric brain tumours.PET imaging can supplement MRI using an amino acid tracer as O-(2-[^{18}F]fluoroethyl-L-tyrosine (FET), L-[methyl- ^{11}C]methionine (MET), or 3,4-dihydroxy-6-[^{18}F]fluoro-L-phenylalamine (FDOPA). 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) is a less useful tracer due to the high uptake in normal grey matter and will not be mentioned further. Four hours of fasting is recommended before tracer injection to ensure stable metabolic conditions. The use of a head holder is recommended to avoid motion artifacts.

Tracer	Dose MBq/kg	Examples of Scan times	Background region (healthy tissue)	Tumour-to background ratio	Physiological uptake
FET	3	20-40 min p.i. or 0-40 min p.i. (dynamic)	Cortical non-affected GM and WM	>1.6 (or >1.8)	Vascular structures, cerebellum, skin, basal ganglia, pineal body, venous anomaly
MET	10	10-30 min p.i. /20-40 min p.i.	Cortical non-affected GM and WM	>1.3	
FDOPA	3	15-45 min p.i.	Contralateral striatum	>1	Basal ganglia, pituitary, skin, pineal body, venous anomaly
			Cortical non-affected GM and WM	>1.6	

p.i.: post injection, GM: grey matter, WM: white matter

Iterative reconstruction should be applied or alternatively filtered back projection. Corrections for attenuation, scatter, randoms, dead time, and decay should be applied. The use of point-spread-function reconstructions may give rise to artefacts and is not recommended. Voxel size < 3mm in all directions and a spatial resolution < 6 mm FWHM is recommended.

PET scans are co-registered to a recent (ideally < 2 weeks) MRI preferentially T1W + contrast or FLAIR. Note that automatic co-registration systems may introduce errors in children. Integration of information obtained by MRI and PET should be performed by diagnostic imaging specialists in close collaboration of each other in order to offer clinicians a more comprehensive array of data. Tracer uptake is reported as maximal tumour-to-background ratio (TBR_{max}) and metabolic active volume. In case of DOPA PET maximal tumor-to-normal striatum ratio (TSRmax) should also be reported. Increased uptake can be seen in inflammatory lesions and after epileptic seizures.
For dynamic FET: an analysis with extraction of tumour time-activity-curves is possible and may be compared to that of healthy brain. The classification into increasing, decreasing or plateau may support the differentiation between inflammatory changes and tumour.